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64. (New) The non-human transgenic mammal of claim 63, wherein the two glycosylation sites modified are Gln 125 and Gln 232 as in SEQ ID NO: 3.

Remarks

Applicant submits the present Preliminary Amendment, which cancels claims 1-26, amends claims 27-36, and adds new claims 37-64. Applicant reserves the right to pursue the original or filed claims in any future continuation or divisional applications. Please consider the above Amendment and following Remarks, which address rejections made by the Examiner in the Final Office Action of the parent application, U.S.S.N. 09/337,079, filed June 21, 1999.

Support for the Amendment

In support of the recitation of "non-mammalian anti-microbial" in claims 32 and 51, Applicants point to page 2, lines 7-9 of the specification, which states:

"In particular, the invention provides methods and reagents for expressing in mammalian cells microbial proteins that have anti-microbial, particularly anti-staphylococcal, activity. The invention provides both altered genes, in which the naturally-occurring microbial sequences have been engineered to allow expression of active protein in desired mammalian cells or tissues, and methods of introducing such altered genes into desired mammalian cells and/or tissues."

Applicants wish to point out that lysozyme and lactoferrin are mammalian proteins and therefore are still excluded from the amended claims. Further support for the expression of non-mammalian microbial proteins having anti-microbial activity can be found in the specification in the definition of "altered gene" at page 6, lines 20-22. Specific *microbial* anti-microbial proteins are listed at page 8, lines 13-24 as follows:

"Those of ordinary skill in the art will appreciate that a significant number of microbial proteins, naturally found in any number of microbial hosts, are known to have anti-microbial activity. In principle, the gene encoding any such protein could be altered in accordance with the present invention. Preferred genes include those encoding anti-staphylococcal activity, for example, β -lytic protease, lysostaphin, -lytic protease, lyt-M, at1ALE-1, zooA. Other preferred anti-microbial peptides or proteins whose genes could be utilized include lysozyme, nisin, muramidases, glucoasminidases, and colicins. (see, for example Shockman and Barrett, *Proc. Natl. Acad. Sci. U. S.A.*, 51:414-421, 1964; Yamada et al., *J. Bacteriol.*, 178:1565-1571, 1996). Particularly preferred are genes

encoding bacteriocins, which are peptide antibiotics that are produced by bacteria and are effective against even closely related species but do not have significant deleterious effects on the species that produces them or on eukaryotic cells. One particularly preferred bacteriocin gene is the lysostaphin gene."

Support for the recitation of "wherein the lysostaphin transgene has been altered to allow expression of an active lysostaphin protein in mammalian cells and tissues" in claims 27 and 32 can be found at page 6, lines 17-28. Support for recitation of "an alteration that disrupts one or more mammalian post-translational processing events" in claims 28 or 33, or "an alteration that adds or removes one or more mammalian post-translational processing sites" in new claim 46 can be found at page 6, lines 26-27 and page 3, lines 1-3. Support for the amendments to claims 29-31 and 34-36 can be found within the definition of "operably linked" at page 7, lines 17-26. Support for "upstream" in claims 31 and 36 can be found at page 7, lines 23-24. Support for "anti-viral" in new claims 41 and 52 can be found at page 15, line 29. Support for "nisins, muramidases, glucoasminidases, and colicins" in new claims 45 and 56 can be found at page 8, lines 18-19. Support for "anti-staphylococcal" in new claims 49 and 57 can be found at page 2, line 8. Support for " β -lytic protease, lysostaphin, α -lytic protease, lyt-M, at1ALE-1, and zooA" in new claims 47 and 58 can be found at page 8, line 17. Support for " β -lytic protease" in new claims 48 and 49 can be found at page 8, line 17. Support for "mammary cells and tissues" in new claim 39 can be found at page 2, lines 9-12. Support for "mammary secretory cells" in new claim 40 can be found at page 2, line 20 to page 3, line 3.

Rejections Under 35 U.S.C. § 112, First Paragraph

In the Final Office Action of the parent application, claims 32-49 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserted that the amendment in claim 32 reciting "wherein the anti-microbial is not lysozyme or lactoferrin" does not have literal or figurative support in the instant specification.

Applicant points out that the claims have been amended to delete this phrase. The broadest claims are now directed to expression of non-mammalian anti-microbial proteins. For example, claim 32 now recites a non-human transgenic mammal, which comprises a transgene including an altered non-mammalian anti-microbial gene, which altered non-mammalian anti-microbial gene differs from a naturally-occurring non-mammalian anti-microbial gene in that the

altered non-mammalian anti-microbial gene contains one or more sequences necessary and sufficient for expression of an active secreted non-mammalian anti-microbial protein by mammalian cells and tissues.

The claimed invention is directed to transgenic mammals encoding transgenes that originate from non-mammalian (e.g., microbial or viral) hosts, as defined at page 7 of the specification. Both lysozyme and lactoferrin are mammalian proteins, which are excluded from the amended claims. Instead, non-mammalian proteins having anti-microbial activity include anti-microbials such as β -lytic protease, lysostaphin, α -lytic protease, lyt-M, at1ALE-1, zooA, and bacteriocins and anti-virals, as described at page 8, lines 13-24 and page 16, lines 8-10. In light of the present amendment, Applicant asserts that the claims are fully supported by the specification and no new matter has been added to the claims.

Claims 27-36 were rejected and claims 37-49 (now new claims 37-64) were newly rejected under 35 U.S.C. § 112, first paragraph on the assertion that the specification does not reasonably provide enablement for a transgenic non-human mammal comprising a transgene encoding any anti-microbial protein in any tissue and/or cell.

The Examiner acknowledged that the specification is enabling for a transgenic non-human mammal whose somatic and germ cells contain a transgene, wherein the transgene comprises a mammary gland specific promoter, a mammary gland specific enhancer, a DNA sequence encoding an active anti-microbial protein wherein the transgenic non-human mammal expresses the transgene in mammary secretory cells such that the active anti-microbial protein is detectable in milk produced by the transgenic non-human mammal. The Examiner further stated that mammary tissue expression of a transgene is fully enabled by the specification. In addition, the Examiner stated that the expression of active anti-microbial proteins in said tissue and the production of said protein in the milk of said transgenic mammal is enabled by the instant specification. The Examiner even acknowledged that the instant specification provides the necessary guidance and overcomes the unpredictability recognized in the art by providing working examples of expression of an anti-microbial transgene in mammary secretory cells. However, the Examiner asserted that the specification does not reasonably provide enablement

for a transgenic non-human mammal comprising a transgene encoding any anti-microbial protein in any tissue or cell of the mammal.

New independent claim 61 (and dependent claims 62-64), which recites a non-human transgenic mammal comprising a transgene encoding lysostaphin, wherein the transgene comprises a nucleic acid sequence encoding lysostaphin operatively linked to at least one mammary expression signal sufficient to direct expression of lysostaphin in mammary cells and tissues, wherein the nucleic acid sequence encoding lysostaphin is modified such that at least one glycosylation site in the lysostaphin coding sequence is disrupted, are clearly allowable in light of the Examiner's comments. However, Applicant disagrees with the rejection of claims 27-36, and challenges that rejection to the extent that it may be applicable to new claims (now claims 37-64) and present arguments below.

The Examiner acknowledged in the Office Action mailed August 29, 2001 that the anti-microbial phenotype produced by transgene expression may be extended to other tissues by expression of an anti-microbial transgene with tissue specific promoters driving expression in that tissue. However, the Examiner argues that at the time the invention was made, the production of transgenic animals was still unpredictable. This is simply not true.

The present application claims priority to provisional application 60/090,175, filed June 22, 1998. As of this recent date, methods of making transgenic animals that express a transgene in a tissue-specific manner by linking a tissue-specific promoter to a transgene were well known. As pointed out in the response to the Office Action mailed January 18, 2001, a number of references were available in the art at the time of the invention that clearly demonstrated the routine use of tissue-specific promoters to direct the tissue-specific expression of a transgene in transgenic mammals. The teachings of those references are reiterated in the table below, in addition to one reference by Su et al.:

TRANSGENIC MAMMAL	TISSUE	PROMOTER	REFERENCE
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TRANSGENIC MAMMAL	TISSUE	PROMOTER	REFERENCE
Mouse	central axons	Purkinje cell specific L7 promoter	Buffo et al. <i>J. Neurosci</i> 1997 Nov 15; 17(22): 8778-91 (Exhibit B)
Mouse	skeletal muscle, liver, and adipose tissue	phosphoenolpyruvate carboxykinase promoter	Guo et al. <i>J. Biol. Chem.</i> 1998 Jun 26;273(26):16487-16493 (Exhibit C)
Mouse	brain	CCK gene promoter	Itoh et al. <i>Dev. Growth Differ.</i> 1998 Aug; 40(4);395-402 (Exhibit D)
Mouse	growth plate of skeletal segments	collagen promoter	Schipani et al. (<i>Proc. Natl. Acad. Sci. U.S.A.</i> 1997 Dec 9; 94(25):13689-94 (Exhibit E)
Mouse	skin	keratin 6 protein regulatory region	Ramirez et al. <i>DNA Cell Biol.</i> 1998 Feb; 17(2):177-185 (Exhibit F)
Mouse	stomach, urinary bladder, ocular lens, and lung cornea	aldehyde dehydrogenase class 3 (ALDH3) promoter ALDH3 promoter	Kays et al. <i>Proc. Natl. Acad. Sci. U.S.A.</i> 1997 Dec 9; 94(25):13594-9, (Exhibit G)
Sheep	mouse keratin promoter	skin and a wide range of other tissues	Su et al. <i>Animal Biotechnol.</i> 9(2):135-147 (1998) Animal and Veterinary Sciences Group, Lincoln University, Canterbury, New Zealand. (Exhibit H)

In considering the above, it cannot be denied that these references demonstrate that at the time of the invention tissue-specific promoters were routinely being used to obtain tissue-specific expression of desired genes in transgenic mammals. Any person skilled in the art would appreciate that once a tissue-specific promoter was identified, it could be reasonably expected to direct tissue-specific expression of any gene in a transgenic mammal by simply inserting it into an expression cassette and using the expression cassette to generate a transgenic mammal. Those skilled in the art at the time of the invention would have appreciated that one tissue-specific promoter (or any mammary gland specific expression signal such as a promoter and an enhancer) could simply be replaced with another tissue-specific promoter to achieve expression in another tissue. In fact, the examples provided in the specification demonstrate the above assertion (that tissue specific expression in a transgenic mammal could be readily obtained at the time of the invention by linking a known tissue-specific promoter to a transgene in the appropriate expression cassette) is true. Specifically, Examples 4 and 5 demonstrate the generation of a transgenic mouse that expresses a non-mammalian anti-microbial in mammary gland tissue, which is active against *S. aureus in vivo*. In order to achieve this result, the inventors simply selected from among a variety of known mammary-specific promoters, e.g., β -lactoglobulin, α -lactalbumen, caseins and whey acidic protein, the β -lactoglobulin promoter. As predicted, use of the β -lactoglobulin promoter resulted in expression of sufficient amounts of the transgene encoded non-mammalian anti-microbial protein, lysostaphin, in the mammary gland of the transgenic mouse to prevent infection in those tissues. Moreover, the use of tissue specific promoters is taught at page 11, first paragraph, of the specification.

Applicant submits that such evidence is sufficient to refute the Examiner's assertions that specific guidance, sufficient to provide a nexus of a proposed transgene construct and the successful use in a transgenic animal, has not been provided. Indeed, what the Examiner holds as unpredictable has been done. Based on the examples provided in the specification, one skilled in the art at the time the invention was made would have recognize that in order to achieve expression in a tissue other than mammary gland, one could simply replace the mammary specific promoter with a promoter capable of driving expression in a tissue other than mammary

The Examiner further questioned how to produce enough of the recombinant protein without inducing an immune response.

Applicant points out that in a transgenic animal, a protein expressed from a transgene *in vivo* will be recognized as “self” and will not produce an allergic response. Whereas immune responses may indeed be generated if an exogenous protein were administered to an animal, or if a transgene is expressed from a viral expression vector that has been introduced into an animal, this is certainly not the case for a protein expressed from a transgene construct in a transgenic animal. In light of these facts, Applicant requests that this aspect of the rejection be withdrawn.

In summary, the specification provides explicit guidance on how to make transgenic mammals that express active anti-microbial proteins in a tissue-specific manner and demonstrates the success of carrying out these methods. The specification further demonstrates that the use of tissue-specific promoters to obtain tissue-specific expression of any chosen transgene was routine at the time of the invention. In light of these arguments, Applicant requests that the rejection to claims 27-49 be withdrawn.

Rejections Under 35 U.S.C. § 102

In the parent case the Examiner withdrew all rejections made under 35 U.S.C. § 102 in view of Deboer et al. (U.S. Patent No. 5,741,957), Maga et al. (*Journal of Food Protection* (1998) 61(1):52-56), or Platneburg et al. (*Transgenic Research* (1994) 3:99-108). With respect to the new matter rejection with respect to the phrase “the anti-microbial gene is not lysozyme or lactoferrin,” this phrase has been deleted from claim 32. As pointed out above, claim 32 has been amended to refer to a non-mammalian anti-microbial gene, which still excludes from the claim lysozyme and lactoferrin, which are mammalian anti-microbial genes.

Rejections Under 35 U.S.C. 103

Claims 27-36 were rejected and claims 37-49 (now new claims 37-64) were newly rejected under 35 U.S.C. 103(a) as being unpatentable over Deboer et al. U.S. Patent No. 5,741,957 in view of Williamson et al. (*Applied and Environmental Microbiology* (March 1994) 60(3):771-776) and Recsei (US Patent 4,931,390). The Examiner stated that it would have been *prima facie* obvious at the time of the claimed invention to use the detailed teachings of Deboer

et al. in creating transgenic non-human mammals, in particular for the expression of anti-microbial proteins which are produced and secreted in the secretory cells of the mammary gland for the treatment of mastitis, wherein the transgene used is the anti-microbial protein lysostaphin, as taught by Williamson et al. and Recsei. Applicants disagree.

Deboer et al. disclose methods of making transgenic mice and transgenic bovines that express active human lactoferrin and/or human lysozyme in their milk (see Examples 19 and 22, and 26). Human lactoferrin and human lysozyme are mammalian anti-microbial proteins and do not fall within the limits of the claims. Williamson et al. disclose expression in a mammalian *in vitro* system (cultured mammalian cells) of the non-mammalian anti-microbial protein, lysostaphin. However, as stated at page 23, lines 3-16 of the specification, the lysostaphin protein produced by this system *is not biologically active*. In support of this assertion, Applicant submits Exhibit A, a publication by Kerr et al. that shows in Figure 2, panel A, that the unaltered lysostaphin protein lacks staphylolytic activity (indicated by the lack of clearing on the lawn of *S. aureus*). Recsei merely discloses the DNA and amino acid sequence of lysostaphin and expression plasmids for transformation of microbial (non-mammalian) hosts.

The combined teachings of these references do not in any way suggest that the generation of a transgenic non-human mammal expressing a non-mammalian anti-microbial protein that would be active *in vivo*. In fact, if one of ordinary skill in the art at the time of the invention were to combine the teachings of these references, the opposite conclusion would be made. The combined references demonstrate that only *mammalian* anti-microbial proteins are biologically active against microbial pathogens in mammalian cells (and non-mammalian anti-microbial proteins are not). Based on these teachings, one would not expect a transgene encoding a non-mammalian anti-microbial protein, e.g., such as the lysostaphin protein disclosed by Recsei, to be active *in vivo*. Indeed, the lysostaphin protein expressed by Williamson et al. is not active in mammalian cells.

Because of the tremendous expense associated with generating transgenic animals, one would not attempt to make a transgenic mammal encoding a lysostaphin protein, or any other non-mammalian anti-microbial protein, unless expression of an active form of the non-mammalian anti-microbial protein in mammalian cells was achieved. This is exactly the

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Respectfully submitted,

VERSION WITH MARKING TO SHOW CHANGES MADE

In the Claims:

Claims 27-36 have been amended as follows.

Claims 1-26 have been canceled.

Claims 37-64 have been added as follows.

27. (Amended) A non-human transgenic [mammalian animal] mammal which comprises a transgene [encoding] including an altered lysostaphin gene, which altered lysostaphin gene differs from naturally-occurring lysostaphin genes in that the altered gene contains one or more sequences necessary and sufficient for expression of an active secreted lysostaphin protein by mammalian cell and tissues.

28. (Amended) The non-human transgenic [mammalian animal] mammal of claim 27 wherein the altered lysostaphin transgene [has been modified for expression of an active form in mammalian cells] comprises an alteration that disrupts one or more mammalian post-translational processing events.

29. (Amended) The non-human transgenic [mammalian animal] mammal of claim 2[7] 8

located 3' to the secretion signal, wherein coding sequence encodes the lysostaphin protein which lysostaphin protein has an amino acid sequence that differs from a naturally-occurring lysostaphin protein in that at least one glycosylation site has been removed results in expression of the lysostaphin protein in mammary cells and tissues.

30. (Amended) The non-human transgenic mammal [gene] of claim 27 wherein the [gene] transgene [encoding lysostaphin is modified] contains nucleotide sequences as in SEQ ID NO: 3, which comprises in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon;

[a eukaryotic promoter;] and

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a coding sequence located 3' to the Kozak expression start site, which coding sequence encodes the lysostaphin protein, which lysostaphin protein has an amino acid sequence that differs from a naturally-occurring lysostaphin protein in that at least one glycosylation site is removed, wherein the operable association expression of the lysostaphin protein in mammary cells and tissues.

31. (Amended) The non-human transgenic [mammalian animal] mammal of claim 27 or 28 wherein the [modified] transgene is inserted into [the] a bovine β -lactoglobulin expression cassette which comprises:

a nucleic acid sequence encoding 4.2 kilobase pairs of the 5'-regulatory region of the bovine β -lactoglobulin gene;

a nucleic acid sequence encoding exons 5, 6, and 7 of the bovine β -lactoglobulin gene;

and

a nucleic acid sequence encoding 2.0 kilobases of 3'-untranslated region of the bovine β -lactoglobulin gene, wherein the 5'-regulatory region is located upstream of exons 5, 6, and 7, and exons 5, 6, and 7 are located upstream of the 3'-untranslated region, wherein the insertion of the altered lysostaphin transgene into the β -lactoglobulin expression cassette results in expression of the lysostaphin transgene in mammary cells and tissues.

32. (Amended) A non-human transgenic [mammalian animal] mammal [which] that comprises a transgene [encoding] including [an] an altered non-mammalian anti-microbial [protein] gene, which altered non-mammalian anti-microbial gene differs from a naturally-occurring non-mammalian anti-microbial gene in that the altered non-mammalian anti-microbial gene contains one or more sequences necessary and sufficient for expression of an active secreted non-mammalian anti-microbial protein by mammalian cells and tissues.

33. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 wherein the alteration to the non-mammalian anti-microbial transgene is an alteration that disrupts one or more mammalian post-translational processing events [has been modified for expression of an active form in mammalian cells].

34. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 wherein the non-mammalian anti-microbial transgene [encoding lysostaphin is modified to comprise] comprises in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon;

[a eukaryotic promoter]

a eukaryotic secretion signal located 3' to the Kozak expression start site; and

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a nucleic acid

sequence located 3' to the secretion signal, the nucleic acid sequence encoding the non-mammalian anti-microbial polypeptide from which at least one glycosylation site in the non-mammalian anti-microbial polypeptide is removed, wherein the operable association polypeptide results in expression of the non-mammalian anti-microbial polypeptide in mammary cells and tissues.

35. (Amended) The non-human transgenic mammal [gene] of claim [32] 37 wherein the [gene encoding the anti-microbial is modified to comprise] non-mammalian anti-microbial transgene encoding the non-mammalian anti-microbial protein is modified to comprise in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon; and;

[a eukaryotic promoter; and]

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a nucleic acid sequence located 3' to the Kozak expression start site, the nucleic acid sequence encoding the non-mammalian anti-microbial polypeptide from which at least one glycosylation site in the non-mammalian anti-microbial polypeptide is removed, wherein the operable association results in expression of the non-mammalian anti-microbial polypeptide in mammary cells and tissues.

36. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 or 33 wherein the [modified] altered non-mammalian anti-microbial transgene is inserted into [the] a bovine β -lactoglobulin expression cassette which comprises:

a nucleic acid sequence encoding 4.2 kilobase pairs of the 5'-regulatory region of the bovine β -lactoglobulin gene;

a nucleic acid sequence encoding exons 5, 6, and 7 of the bovine β -lactoglobulin gene;
and

a nucleic acid sequence encoding 2.0 kilobases of 3'-untranslated region of the bovine β -lactoglobulin gene,

wherein in the β -lactoglobulin expression cassette the 5'-regulatory region of the bovine- β -lactoglobulin gene is located upstream of exons 5, 6, and 7, and exons 5, 6, and 7 are located upstream of the 3'untranslated region, wherein the insertion of the altered transgene into the β -lactoglobulin expression cassette results in expression of the transgene in mammary cells and tissues.

Please add the following new claims.

37. (New) The non-human transgenic mammal of claim 27 or 32, wherein the alteration to the lysostaphin transgene is an alteration that adds or removes one or more mammalian post-translational processing sites.
38. (New) The non-human transgenic mammal of claim 28 or 33, wherein the alteration comprises a disruption of at least one glycosylation site.
39. (New) The non-human transgenic mammal of claim 27 or 32, wherein the mammalian cells and tissues comprise mammary cells and tissues.
40. (New) The non-human transgenic mammal of claim 39, wherein the mammary cells and tissues comprise mammary secretory cells and tissues.
41. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes an anti-viral peptide or protein.
42. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a microbial peptide or protein.
43. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a prokaryotic peptide or protein.

44. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a bacterial peptide or protein.
45. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial is selected from the group consisting of nisins, muramidases, glucoasminidases, endopeptidases, and colicins.
46. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial is an anti-staphylococcal.
47. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is selected from the group consisting of β -lytic protease, lysostaphin, α -lytic protease, lyt-M, at 1ALE-1, and zooA.
48. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is β -lytic protease.
49. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is lysostaphin.
50. (New) A non-human transgenic mammal comprising a transgene encoding a non-mammalian anti-microbial protein, wherein the transgene comprises a nucleic acid sequence encoding the non-mammalian anti-microbial protein operatively linked to a tissue-specific promoter sufficient to direct expression of the non-mammalian antimicrobial protein in mammalian cells and tissues, wherein the nucleic acid sequence encoding the non-mammalian anti-microbial protein is modified such that at least one glycosylation site in the non-mammalian anti-microbial protein coding sequence is disrupted.
51. (New) The non-human transgenic mammal of claim 50, wherein the transgene encoding the non-mammalian anti-microbial protein is further operatively linked to a sequence encoding a signal peptide such that the lysostaphin polypeptide is secreted.
52. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes an anti-viral peptide or protein.

53. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a microbial peptide or protein.
54. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a prokaryotic peptide or protein.
55. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a bacterial peptide or protein.
56. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial is selected from the group consisting of nisins, muramidases, glucoasminidases, endopeptidases, and colicins.
57. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial is an anti-staphylococcal.
58. (New) The non-human transgenic mammal of claim 57, wherein the anti-staphylococcal is selected from the group consisting of β -lytic protease, lysostaphin, α -lytic protease, lyt-M, at 1ALE-1, and zooA.
59. (New) The non-human transgenic mammal of claim 57, wherein the anti-staphylococcal is β -lytic protease.
60. (New) The non-human transgenic mammal of claim 57, wherein the anti-staphylococcal is lysostaphin.
61. (New) A non-human transgenic mammal comprising a transgene encoding lysostaphin, wherein the transgene comprises a nucleic acid sequence encoding lysostaphin operatively linked to at least one mammary expression signal sufficient to direct expression of lysostaphin in mammary cells and tissues, wherein the nucleic acid sequence encoding lysostaphin is modified such that at least one glycosylation site in the lysostaphin coding sequence is disrupted.
62. (New) The non-human transgenic mammal of claim 61, wherein the lysostaphin coding sequence is further operatively linked to a sequence encoding a signal peptide such that the lysostaphin polypeptide is secreted from the mammalian cells.

63. (New) The non-human transgenic mammal of claim 61, wherein two glycosylation sites are modified.

64. (New) The non-human transgenic mammal of claim 63, wherein the two glycosylation sites modified are Gln 125 and Gln 232 as in SEQ ID NO: 3.--

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VERSION WITH MARKING TO SHOW CHANGES MADE

In the Claims:

Claims 27-36 have been amended as follows.

27-64

Claims 1-26 have been canceled.

Claims 37-64 have been added as follows.

27. (Amended) A non-human transgenic [mammalian animal] mammal which comprises a transgene [encoding] including an altered lysostaphin gene, which altered lysostaphin gene differs from naturally-occurring lysostaphin genes in that the altered gene contains one or more sequences necessary and sufficient for expression of an active secreted lysostaphin protein by mammalian cell and tissues.

28. (Amended) The non-human transgenic [mammalian animal] mammal of claim 27 wherein the altered lysostaphin transgene [has been modified for expression of an active form in mammalian cells] comprises an alteration that disrupts one or more mammalian post-translational processing events.

29. (Amended) The non-human transgenic [mammalian animal] mammal of claim 2[7] 8 wherein the transgene [encoding lysostaphin is modified] contains nucleotide sequences as in SEQ ID NO: 3, which comprises in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon;

[a eukaryotic promoter]

a eukaryotic secretion signal located 3' to the Kozak expression start site; and

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a coding sequence

located 3' to the secretion signal, wherein coding sequence encodes the lysostaphin protein which lysostaphin protein has an amino acid sequence that differs from a naturally-occurring lysostaphin protein in that at least one glycosylation site has been removed results in expression of the lysostaphin protein in mammary cells and tissues.

30. (Amended) The non-human transgenic mammal [gene] of claim 27 wherein the [gene] transgene [encoding lysostaphin is modified] contains nucleotide sequences as in SEQ ID NO: 3, which comprises in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon;

[a eukaryotic promoter;] and

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a coding sequence located 3' to the Kozak expression start site, which coding sequence encodes the lysostaphin protein, which lysostaphin protein has an amino acid sequence that differs from a naturally-occurring lysostaphin protein in that at least one glycosylation site is removed, wherein the operable association expression of the lysostaphin protein in mammary cells and tissues.

31. (Amended) The non-human transgenic [mammalian animal] mammal of claim 27 or 28 wherein the [modified] transgene is inserted into [the] a bovine β -lactoglobulin expression cassette which comprises:

a nucleic acid sequence encoding 4.2 kilobase pairs of the 5'-regulatory region of the bovine β -lactoglobulin gene;

a nucleic acid sequence encoding exons 5, 6, and 7 of the bovine β -lactoglobulin gene;

and

a nucleic acid sequence encoding 2.0 kilobases of 3'-untranslated region of the bovine β -lactoglobulin gene, wherein the 5'-regulatory region is located upstream of exons 5, 6, and 7, and exons 5, 6, and 7 are located upstream of the 3'-untranslated region, wherein the insertion of the altered lysostaphin transgene into the β -lactoglobulin expression cassette results in expression of the lysostaphin transgene in mammary cells and tissues.

32. (Amended) A non-human transgenic [mammalian animal] mammal [which] that comprises a transgene [encoding] including [an] an altered non-mammalian anti-microbial [protein] gene, which altered non-mammalian anti-microbial gene differs from a naturally-occurring non-mammalian anti-microbial gene in that the altered non-mammalian anti-microbial gene contains one or more sequences necessary and sufficient for expression of an active secreted non-mammalian anti-microbial protein by mammalian cells and tissues.

33. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 wherein the alteration to the non-mammalian anti-microbial transgene is an alteration that disrupts one or more mammalian post-translational processing events [has been modified for expression of an active form in mammalian cells].

34. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 wherein the non-mammalian anti-microbial transgene [encoding lysostaphin is modified to comprise] comprises in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon;

[a eukaryotic promoter]

a eukaryotic secretion signal located 3' to the Kozak expression start site; and

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a nucleic acid

sequence located 3' to the secretion signal, the nucleic acid sequence encoding the non-mammalian anti-microbial polypeptide from which at least one glycosylation site in the non-mammalian anti-microbial polypeptide is removed, wherein the operable association polypeptide results in expression of the non-mammalian anti-microbial polypeptide in mammary cells and tissues.

35. (Amended) The non-human transgenic mammal [gene] of claim [32] 37 wherein the [gene encoding the anti-microbial is modified to comprise] non-mammalian anti-microbial transgene encoding the non-mammalian anti-microbial protein is modified to comprise in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon; and;

[a eukaryotic promoter; and]

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a nucleic acid sequence located 3' to the Kozak expression start site, the nucleic acid sequence encoding the non-mammalian anti-microbial polypeptide from which at least one glycosylation site in the non-mammalian anti-microbial polypeptide is removed, wherein the operable association results in expression of the non-mammalian anti-microbial polypeptide in mammary cells and tissues.

36. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 or 33 wherein the [modified] altered non-mammalian anti-microbial transgene is inserted into [the] a bovine β -lactoglobulin expression cassette which comprises:

a nucleic acid sequence encoding 4.2 kilobase pairs of the 5'-regulatory region of the bovine β -lactoglobulin gene;

a nucleic acid sequence encoding exons 5, 6, and 7 of the bovine β -lactoglobulin gene;
and

a nucleic acid sequence encoding 2.0 kilobases of 3'-untranslated region of the bovine β -lactoglobulin gene,

wherein in the β -lactoglobulin expression cassette the 5'-regulatory region of the bovine- β -lactoglobulin gene is located upstream of exons 5, 6, and 7, and exons 5, 6, and 7 are located upstream of the 3'untranslated region, wherein the insertion of the altered transgene into the β -lactoglobulin expression cassette results in expression of the transgene in mammary cells and tissues.

Please add the following new claims.

37. (New) The non-human transgenic mammal of claim 27 or 32, wherein the alteration to the lysostaphin transgene is an alteration that adds or removes one or more mammalian post-translational processing sites.

38. (New) The non-human transgenic mammal of claim 28 or 33, wherein the alteration comprises a disruption of at least one glycosylation site.

39. (New) The non-human transgenic mammal of claim 27 or 32, wherein the mammalian cells and tissues comprise mammary cells and tissues.

40. (New) The non-human transgenic mammal of claim 39, wherein the mammary cells and tissues comprise mammary secretory cells and tissues.

41. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes an anti-viral peptide or protein.

42. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a microbial peptide or protein.

43. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a prokaryotic peptide or protein.

44. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a bacterial peptide or protein.

45. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial is selected from the group consisting of nisins, muramidases, glucoasminidases, endopeptidases, and colicins.

46. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial is an anti-staphylococcal.

47. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is selected from the group consisting of β -lytic protease, lysostaphin, α -lytic protease, lyt-M, at 1ALE-1, and zooA.

48. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is β -lytic protease.

49. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is lysostaphin.

50. (New) A non-human transgenic mammal comprising a transgene encoding a non-mammalian anti-microbial protein, wherein the transgene comprises a nucleic acid sequence encoding the non-mammalian anti-microbial protein operatively linked to a tissue-specific promoter sufficient to direct expression of the non-mammalian antimicrobial protein in mammalian cells and tissues, wherein the nucleic acid sequence encoding the non-mammalian anti-microbial protein is modified such that at least one glycosylation site in the non-mammalian anti-microbial protein coding sequence is disrupted.

51. (New) The non-human transgenic mammal of claim 50, wherein the transgene encoding the non-mammalian anti-microbial protein is further operatively linked to a sequence encoding a signal peptide such that the lysostaphin polypeptide is secreted.

52. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes an anti-viral peptide or protein.

53. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a microbial peptide or protein.

54. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a prokaryotic peptide or protein.

55. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a bacterial peptide or protein.

56. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial is selected from the group consisting of nisins, muramidases, glucoasminidases, endopeptidases, and colicins.

57. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial is an anti-staphylococcal.

58. (New) The non-human transgenic mammal of claim 57, wherein the anti-staphylococcal is selected from the group consisting of β -lytic protease, lysostaphin, α -lytic protease, lyt-M, at 1ALE-1, and zooA.

59. (New) The non-human transgenic mammal of claim 57, wherein the anti-staphylococcal is β -lytic protease.

60. (New) The non-human transgenic mammal of claim 57, wherein the anti-staphylococcal is lysostaphin.

61. (New) A non-human transgenic mammal comprising a transgene encoding lysostaphin, wherein the transgene comprises a nucleic acid sequence encoding lysostaphin operatively linked to at least one mammary expression signal sufficient to direct expression of lysostaphin in mammary cells and tissues, wherein the nucleic acid sequence encoding lysostaphin is modified such that at least one glycosylation site in the lysostaphin coding sequence is disrupted.

62. (New) The non-human transgenic mammal of claim 61, wherein the lysostaphin coding sequence is further operatively linked to a sequence encoding a signal peptide such that the lysostaphin polypeptide is secreted from the mammalian cells.

63. (New) The non-human transgenic mammal of claim 61, wherein two glycosylation sites are modified.

64. (New) The non-human transgenic mammal of claim 63, wherein the two glycosylation sites modified are Gln 125 and Gln 232 as in SEQ ID NO: 3.--

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VERSION WITH MARKING TO SHOW CHANGES MADE

In the Claims:

Claims 27-36 have been amended as follows.

Claims 1-26 have been canceled.

Claims 37-64 have been added as follows.

I 27-31 (37-40) 41-44
II 32-36 (37-40) 41-44
III 50-60 and species

27. (Amended) A non-human transgenic [mammalian animal] mammal which comprises a transgene [encoding] including an altered lysostaphin gene, which altered lysostaphin gene differs from naturally-occurring lysostaphin genes in that the altered gene contains one or more sequences necessary and sufficient for expression of an active secreted lysostaphin protein by mammalian cell and tissues.

28. (Amended) The non-human transgenic [mammalian animal] mammal of claim 27 wherein the altered lysostaphin transgene [has been modified for expression of an active form in mammalian cells] comprises an alteration that disrupts one or more mammalian post-translational processing events.

29. (Amended) The non-human transgenic [mammalian animal] mammal of claim 27 wherein the transgene [encoding lysostaphin is modified] contains nucleotide sequences as in SEQ ID NO: 3, which comprises in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon;

[a eukaryotic promoter]

a eukaryotic secretion signal located 3' to the Kozak expression start site; and

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene]

located 3' to the secretion signal, wherein coding sequence encodes the lysostaphin protein which lysostaphin protein has an amino acid sequence that differs from a naturally-occurring lysostaphin protein in that at least one glycosylation site has been removed results in expression of the lysostaphin protein in mammary cells and tissues.

30. (Amended) The non-human transgenic mammal [gene] of claim 27 wherein the [gene] transgene [encoding lysostaphin is modified] contains nucleotide sequences as in SEQ ID NO: 3, which comprises in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon;

[a eukaryotic promoter;] and

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a coding sequence located 3' to the Kozak expression start site, which coding sequence encodes the lysostaphin protein, which lysostaphin protein has an amino acid sequence that differs from a naturally-occurring lysostaphin protein in that at least one glycosylation site is removed, wherein the operable association expression of the lysostaphin protein in mammary cells and tissues.

31. (Amended) The non-human transgenic [mammalian animal] mammal of claim 27 or 28 wherein the [modified] transgene is inserted into [the] a bovine β -lactoglobulin expression cassette which comprises:

a nucleic acid sequence encoding 4.2 kilobase pairs of the 5'-regulatory region of the bovine β -lactoglobulin gene;

a nucleic acid sequence encoding exons 5, 6, and 7 of the bovine β -lactoglobulin gene;

and

a nucleic acid sequence encoding 2.0 kilobases of 3'-untranslated region of the bovine β -lactoglobulin gene, wherein the 5'-regulatory region is located upstream of exons 5, 6, and 7, and exons 5, 6, and 7 are located upstream of the 3'-untranslated region, wherein the insertion of the altered lysostaphin transgene into the β -lactoglobulin expression cassette results in expression of the lysostaphin transgene in mammary cells and tissues.

32. (Amended) A non-human transgenic [mammalian animal] mammal [which] that comprises a transgene [encoding] including [an] an altered non-mammalian anti-microbial [protein] gene, which altered non-mammalian anti-microbial gene differs from a naturally-occurring non-mammalian anti-microbial gene in that the altered non-mammalian anti-microbial gene contains one or more sequences necessary and sufficient for expression of an active secreted non-mammalian anti-microbial protein by mammalian cells and tissues.

33. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 wherein the alteration to the non-mammalian anti-microbial transgene is an alteration that disrupts one or more mammalian post-translational processing events [has been modified for expression of an active form in mammalian cells].

34. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 wherein the non-mammalian anti-microbial transgene [encoding lysostaphin is modified to comprise] comprises in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon;

[a eukaryotic promoter]

a eukaryotic secretion signal located 3' to the Kozak expression start site; and

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a nucleic acid

sequence located 3' to the secretion signal, the nucleic acid sequence encoding the non-mammalian anti-microbial polypeptide from which at least one glycosylation site in the non-mammalian anti-microbial polypeptide is removed, wherein the operable association polypeptide results in expression of the non-mammalian anti-microbial polypeptide in mammary cells and tissues.

35. (Amended) The non-human transgenic mammal [gene] of claim [32] 37 wherein the [gene encoding the anti-microbial is modified to comprise] non-mammalian anti-microbial transgene encoding the non-mammalian anti-microbial protein is modified to comprise in operable association:

a eukaryotic mammary specific promoter located 5' to the transgene;

a eukaryotic start codon located 3' to the eukaryotic promoter;

[the] a Kozak expression start site consensus sequence located 3' to the eukaryotic promoter and including the eukaryotic start codon; and;

[a eukaryotic promoter; and]

[the lysostaphin gene from which two glycosylation sites in the lysostaphin gene from which two glycosylation sites in the lysostaphin gene were removed] a nucleic acid sequence located 3' to the Kozak expression start site, the nucleic acid sequence encoding the non-mammalian anti-microbial polypeptide from which at least one glycosylation site in the non-mammalian anti-microbial polypeptide is removed, wherein the operable association results in expression of the non-mammalian anti-microbial polypeptide in mammary cells and tissues.

36. (Amended) The non-human transgenic [mammalian animal] mammal of claim 32 or 33 wherein the [modified] altered non-mammalian anti-microbial transgene is inserted into [the] a bovine β -lactoglobulin expression cassette which comprises:

a nucleic acid sequence encoding 4.2 kilobase pairs of the 5'-regulatory region of the bovine β -lactoglobulin gene;

a nucleic acid sequence encoding exons 5, 6, and 7 of the bovine β -lactoglobulin gene;
and

a nucleic acid sequence encoding 2.0 kilobases of 3'-untranslated region of the bovine β -lactoglobulin gene,

wherein in the β -lactoglobulin expression cassette the 5'-regulatory region of the bovine- β -lactoglobulin gene is located upstream of exons 5, 6, and 7, and exons 5, 6, and 7 are located upstream of the 3'untranslated region, wherein the insertion of the altered transgene into the β -lactoglobulin expression cassette results in expression of the transgene in mammary cells and tissues.

Please add the following new claims.

37. (New) The non-human transgenic mammal of claim 27 or 32, wherein the alteration to the lysostaphin transgene is an alteration that adds or removes one or more mammalian post-translational processing sites.

38. (New) The non-human transgenic mammal of claim 28 or 33, wherein the alteration comprises a disruption of at least one glycosylation site.

39. (New) The non-human transgenic mammal of claim 27 or 32, wherein the mammalian cells and tissues comprise mammary cells and tissues.

40. (New) The non-human transgenic mammal of claim 39, wherein the mammary cells and tissues comprise mammary secretory cells and tissues.

41. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes an anti-viral peptide or protein.

42. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a microbial peptide or protein.

43. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a prokaryotic peptide or protein.

44. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial gene encodes a bacterial peptide or protein.
45. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial is selected from the group consisting of nisins, muramidases, glucoasminidases, endopeptidases, and colicins.
46. (New) The non-human transgenic mammal of claim 32, wherein the non-mammalian anti-microbial is an anti-staphylococcal.
47. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is selected from the group consisting of β -lytic protease, lysostaphin, α -lytic protease, lyt-M, at 1ALE-1, and zooA.
48. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is β -lytic protease.
49. (New) The non-human transgenic mammal of claim 46, wherein the anti-staphylococcal is lysostaphin.
50. (New) A non-human transgenic mammal comprising a transgene encoding a non-mammalian anti-microbial protein, wherein the transgene comprises a nucleic acid sequence encoding the non-mammalian anti-microbial protein operatively linked to a tissue-specific promoter sufficient to direct expression of the non-mammalian antimicrobial protein in mammalian cells and tissues, wherein the nucleic acid sequence encoding the non-mammalian anti-microbial protein is modified such that at least one glycosylation site in the non-mammalian anti-microbial protein coding sequence is disrupted.
51. (New) The non-human transgenic mammal of claim 50, wherein the transgene encoding the non-mammalian anti-microbial protein is further operatively linked to a sequence encoding a signal peptide such that the lysostaphin polypeptide is secreted.
52. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes an anti-viral peptide or protein.

53. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a microbial peptide or protein.

54. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a prokaryotic peptide or protein.

55. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial gene encodes a bacterial peptide or protein.

56. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial is selected from the group consisting of nisins, muramidases, glucoasminidases, endopeptidases, and colicins.

57. (New) The non-human transgenic mammal of claim 50, wherein the non-mammalian anti-microbial is an anti-staphylococcal.

58. (New) The non-human transgenic mammal of claim 57, wherein the anti-staphylococcal is selected from the group consisting of β -lytic protease, lysostaphin, α -lytic protease, lyt-M, at 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 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63. (New) The non-human transgenic mammal of claim 61, wherein two glycosylation sites are modified.

64. (New) The non-human transgenic mammal of claim 63, wherein the two glycosylation sites modified are Gln 125 and Gln 232 as in SEQ ID NO: 3.--

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